Diagnostic value of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT in primary liver cancer: A systematic review and meta-analysis

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Abstract

Objective: To conduct a meta-analysis of the diagnostic efficacy of fluorine-18-fluorodeoxyglucose (^{18}F-FDG) and gallium-68-labeled fibroblast-activation protein inhibitor (^{68}Ga-FAPI) positron emission tomography/computed tomography (PET/CT) for primary liver cancer based on existing clinical evidence. **Materials and Methods:** Meta-analysis was carried out according to PRISMA reporting specification. The clinical studies in PubMed/Medline, Embase and the Cochrane Library database were retrieved from the establishment to September 2022. Two researchers independently conducted literature screening and data extraction, evaluated the risk of bias according to QUADAS-2, conducted meta-analysis using Meta Disc 1.4 and Stata15.1 software, and calculated the summarized sensitivity (SEN), specificity (SPE), positive likelihood ratio (+LR), negative likelihood ratio (-LR), and diagnostic odds ratio (DOR). The diagnostic performance of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT for primary liver cancer was compared using summarized receiver operating characteristic (SROC) curve and area under curve (AUC). **Results:** Four original studies on ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT in the diagnosis of primary liver cancer were included, including 159 intrahepatic lesions in 106 patients. Taking lesions as a unit, in four original studies, the pooled results of ^{18}F-FDG PET/CT diagnosis of primary liver cancer were Sen=0.5 (95% CI:95% CI: 0.41-0.59), Spe=0.87 (95% CI: 0.52-0.98), AUC=0.58 (95% CI:0.53-0.62); The pooled results of ^{68}Ga-FAPI PET/CT in the diagnosis of primary liver cancer, Sen=0.5 (95% CI: 0.41-0.59), Spe=0.87 (95%CI:0.52-0.98), AUC=0.58 (95% CI:0.53-0.62). Besides, the Sen of ^{68}Ga-FAPI PET/CT in the diagnosis of primary liver cancer was higher than that of ^{18}F-FDG PET/CT (Z=2.323, P=0.02), the difference was statistically significant. **Conclusions:** Gallium-68-FAPI PET/CT is a promising tool. Compared with ^{18}F-FDG, ^{68}Ga-FAPI has higher sensitivity to detect more lesions in primary liver cancer and metastatic lesions, and has high performance in the diagnosis of primary liver cancer.

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Introduction

Liver cancer is the third most common cause of cancer-related death worldwide [1]. The high mortality rate of liver cancer indicates the inefficiency of current strategies for evaluating and treating it [2]. Primary liver cancer includes two main histological subtypes: hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA). Hepatocellular carcinoma and intrahepatic cholangiocarcinoma (ICC) account for approximately 80% and 15% [3]. Imaging plays an important role in diagnosis, initial staging, evaluation of treatment response, and detection of recurrence. At present, conventional imaging modalities, including ultrasonography, contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI). While ultrasonography is recommended as an initial surveillance tool for HCC in patients with liver cirrhosis according current practice guidelines, it is limited in its poor performance dropping for small nodule detection [4]. The sensitivity of contrast enhanced ultrasound (CEUS) for the diagnosis of HCC in cirrhosis is only 62% [5]. Contrastingly, the sensitivity of CT or MRI for detecting HCC in patients with cirrhosis ranges between 68% and 88% [6]. While these methods are superior to ultrasonography, they can be further improved.

Currently, fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) is increasingly being recognized as an effective diagnostic imaging tool for cancer. However, ^{18}F-FDG PET/CT has a similar performance in the detection of HCC and CCA with a sensitivity of 68% for HCC, which is close to that of CT or MRI imaging. The poor sensitivity of ^{18}F-FDG PET/CT in detecting HCC could be attributed

to the variable ^{18}F-FDG uptake in HCC [7-9]. The variable uptake could mask some malignant lesions with similar uptake in normal liver tissue and raises the false-negative rate. Specifically, it is likely attributed to the different expresses of glucose transporters in HCC cells, which is closely related to the degree of differentiation and hypoxia of HCC cells [10]. Cholangiocarcinoma have different glucose-regulating mechanisms from those of HCC [11]. There is a significant association between the expression of glucose transporter 1 and hexokinase II with ^{18}F-FDG uptake of CCA [12]. In addition, ^{18}F-FDG PET/CT has poor value for the detection of small HCC lesions [13].

Therefore, there is an urgent need to find a new method with high sensitivity and specificity to diagnose and evaluate liver cancer. Gallium-68-FAPI is a promising radiotracer to detect malignant tumors and it has been used to characterize various malignant tumors [14, 15]. Specifically, ^{68}Ga-FAPI, ^{68}Ga-labelled fibroblast activating protein inhibitor was developed to evaluate fibroblast activation in oncological imaging, with fibroblast activating proteins being highly expressed in cancer-associated fibroblasts (CAF) in various epithelial carcinomas. Cancer-associated fibroblasts are one of the most critical components of the tumor microenvironment, creating a favorable microenvironment for tumor growth, invasion and metastasis [16]. Therefore, fibroblast activation could be a unique signature of the liver microenvironment associated with aggressive tumor behavior. Hepatocellular carcinoma is strongly associated with liver fibrosis; specifically, 80%-90% of HCC develop in fibrotic or cirrhotic livers [17]. Cancer-associated fibroblast is a tumor with a highly desmoplastic microenvironment, which has abundant CAF [18]. Therefore, ^{68}Ga-FAPI may visualizing liver cancer including HCC and CCA by targeting CAF that are abundant in the tumour microenvironment. At present, it is not uncommon for application of ^{68}Ga-FAPI PET/CT in the diagnosis and efficacy evaluation of liver cancer. Increasing studies reported higher ^{68}Ga-FAPI PET/CT uptake in hepatic tumors and its superior sensitivity for detecting hepatic malignancies compared with ^{18}F-FDG PET/CT. Furthermore, some studies recently demonstrated that ^{68}Ga-FAPI PET/CT was superior to ^{18}F-FDG PET/CT for detecting primary and metastatic lesions in patients with various cancer types, inluding liver cancer. In addition, other several new tracers also have been developed and applied for HCC detection, including carbon-11 (^{11}C)-acetate, ^{11}C-choline, ^{68}Ga-prostate-specific membrane antigen (PSMA) [19-21]. However, FAPI PET imaging may appears to show a better performance among currently available tracers in detecting liver malignancies. Although there is not sufficient evidence yet suggesting that ^{68}Ga-FAPI PET/CT is superior to ^{18}F-FDG PET/CT in the diagnosis and evaluation of liver cancer, ^{68}Ga-FAPI PET/CT has a good application prospect for the disease staging, detection of the spread and recurrence of disease, therapeutic evaluation based on current research and leads to precise treatment, especially combined with existing multiple imaging technologies.

At present, ^{68}Ga-FAPI PET/CT for diagnosis of liver cancer has been gradually undergoing clinical trials in some centers to evaluate its feasibility and efficacy. However, due to the small sample size, population heterogeneity and different results, there are few systematic reviews or meta-analysis studies on the diagnosing value of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT for liver cancer in the published literature. This study will meta-analyze the current published clinical studies on the diagnosing value of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT for liver cancer, in the hopes of providing evidence-based medicine of ^{68}Ga-FAPI PET/CT in the diagnosis and evaluation of liver cancer.

Materials and Methods

This study is reported in agreement with the Preferred Reporting Items for a Systematic Review and Meta-Analysis (PRISMA) statement [22]. No ethical approval or informed consent was required.

Search strategy

A comprehensive search of records through the PubMed/Medline, Embase and the Cochrane Library database were carried out to find relevant retrospective or prospective published articles on the diagnostic performance of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT in patients with primary hepatic tumours. The following search algorithm was used: (A) 'PET' OR 'positron emission tomography' OR 'FDG' OR 'fluorodeoxyglucose' AND (B) 'FAPI' OR'FAP' OR'fibroblast'AND (C)'LiverNeoplasms'OR 'Liver tumors' OR 'Liver cancer 'OR' Livermalignancy'OR'hepatictumours'OR'hepatic carcinoma'. The search was carried out from inception to 30 September 2022 without language restriction.

Study selection

Two authors independently screened the literatures. The inclusion criteria: 1)No less than 10 patients with suspected, newly diagnosed, or previously treated liver cancer (including HCC and/or CCA); have the definitive diagnosis by histopathologic or radiographic follow-up. 2) Patients underwent both ^{18}F-FDG and ^{68}Ga-FAPI PET/CT examinations within 1 week before surgical treatment. 3) All patients provided informed consent and assent according to the guidelines of the Clinical Research Ethics Committee. 4) The articles provide enough raw data to complete a 2×2 contingency table [True Positives (TP), False Positives (FP), False Negatives (FN), True Negatives (TN)].

Exclusion criteria: 1) Out of the scope of the present review and meta-analysis. 2) Duplicate published studies, conferences, meta-analyses, reviews, case reports, brief communications, abstracts and letters to the editor. 3) In the case of publications from the same research group/institution that presented significant overlap in terms of aim(s) and population, the study with the largest cohort was included. Disagreements were resolved in a consensus meeting.

Data extraction

For each study, we collected the following information: authors, year of publication, study design (prospective, retrospective), patient characteristics (type and number of patients, age, sex ratio, number of intrahepatic lesions, Cirrhosis, AFP), 2×2 tabular data (TP, FP, FN and TN) based on

intrahepatic lesions, TBR and maximum standardized uptake value (SUVmax) of ^{18}F-FDG and ^{68}Ga-FAPI PET/CT in intrahepatic lesions, and the distant metastasis. The SUVmax was used to evaluate tracer uptake in primary tumours, lymph nodes, and distant metastases. The target-to-background ratio (TBR) of each primary tumour was calculated by dividing the SUVmax of the lesion by the SUVmean of normal background liver.

Quality assessment

The quality of the studies included in the meta-analysis was assessed according to the revised 'Quality Assessment of Diagnostic Accuracy Studies' tool (QUADAS-2) [23]. The latter was used to assess the risk of bias for the following criteria: patient selection, index test, reference test and flow/timing whereas applicability concerns were assessed for patient selection, index test and reference test.

Statistical analysis

Meta-Disc 1.4 and Stata 15.1 software were used for statistical analysis, and the Spearman correlation coefficient was used to test whether there was a threshold effect; Pooled sensitivities, specificities, positive likelihood ratios, negative likelihood ratios, diagnostic odds ratios, and their 95% confidence intervals (CI) were calculated for ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT, respectively, based on a bivariate mixed-effects model); A summary receiver operating characteristic curve (SROC) was drawn, the area under the curve (AUROC) was calculated, and the Z-test was used to compare the diagnostic accuracy of the two tests. The evaluation of heterogeneity between studies is based on I^2 and Q test statistics. $I^2 \geq 50\%$ or $P<0.01$ means there is statistical heterogeneity. If the heterogeneity is large, analyze the source of heterogeneity and conduct Subgroup analysis and meta-regression analysis. Publication bias was determined using the Deeks funnel plot test, pooled analysis of SUVmax and TBR uptake by the two tracers in intrahepatic lesions were performed, and forest plots were drawn.

Results

Literature search

The comprehensive computer literature search from the Pub Med/Medline, Embaseand the Cochrane Library database yielded a total of 295 articles. Sixty three duplicate articles were excluded. After reviewing titles and abstracts, 192 articles were excluded as follows: 51 were irrelevant articles; 20 were reviews, 19 were editorials or letters and 102 were case reports. Then, 40 articles were selected and retrieved in full-text version. According to the inclusion and exclusion criteria of this study design, 36 articles were excluded. Finally, according to the literature quality assessment, a total of 4 articles were included [24-27], as shown in Figure 1.

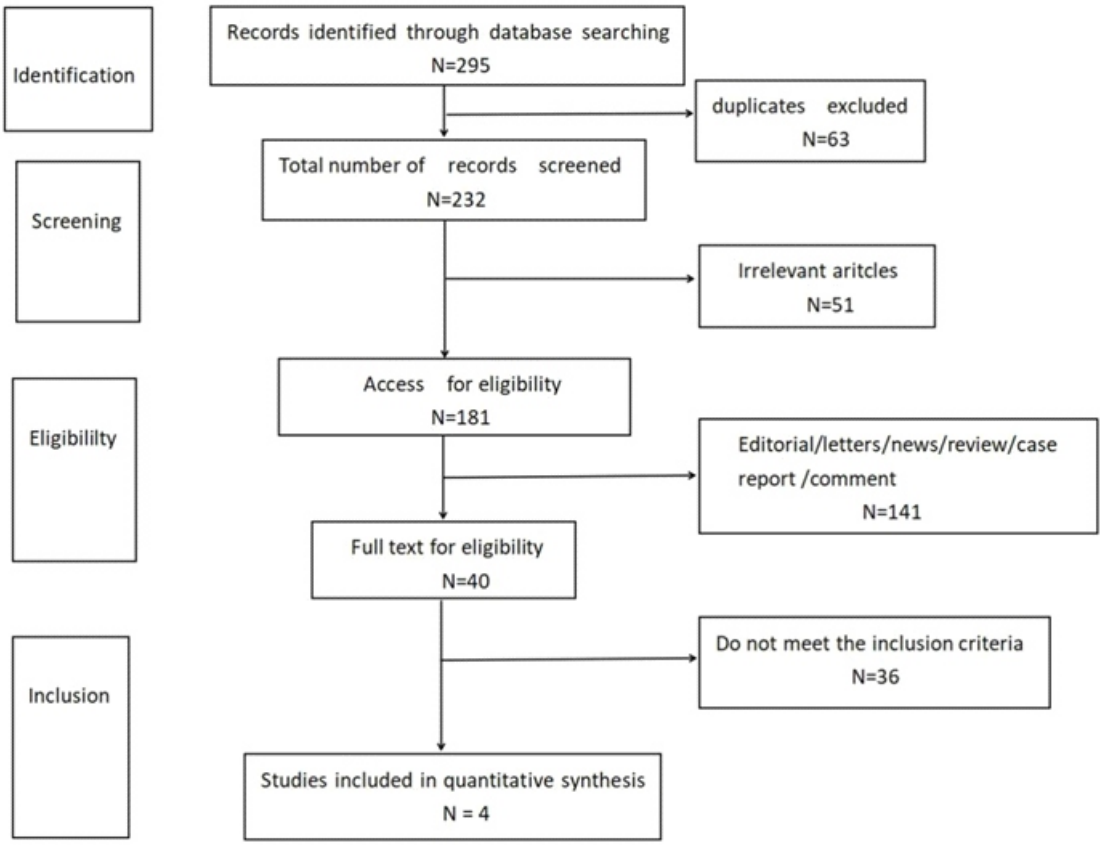

Figure 1. Flowchart of literature screening.

Study and patient characteristics

A total of 4 articles, and 98 patients were included for analysis. Includes 3 retrospective studies [24-26], one prospective study [27]. Only HCC patients were included in [25], and the other three included HCC and CAA. The patients included: Suspected primary liver cancer by other examinations, in order to determine the treatment plan, restaging after treatment, suspected recurrence. All articles describe the uptake of both tracers in primary intrahepatic lesions. Only in two studies [24, 26] the uptake of both tracers in distant metastases was investigated in detail, and a study [27] only outlined the uptake values in extrahepatic lesions in two CCA patients. Two studies [25, 27] investigated the correlation between tumor differentiation type and tracer uptake, and tumor size and tracer uptake were also investigated in Lunxiu Qin et al. [25]. The characteristics of the studies are shown in Tables 1-3.

Methodological quality of studies

Patient selection was the main source of bias among the 4 studies selected for the meta-analysis (Figure 2). One study did not include consecutive or random cases and it did not analyze all included cases. The overall risk of bias of the included articles is relatively small, and applicability should not be overly concerned.

Tables 1-3. *Basic characteristics of the included studies.*

Author	Year	Study	Patients (M/W)	Olds (yr)	Diagnosis standard	Cirrhosis	AFP (>20ng/mL)	Scan interval
Dheeratama Siripongsatian	2022	retrospective	27 (21:6)	68 (60-74)	Histopathologic or MRI	NR	NR	<1 Week
LunxiuQin	2021	retrospective	25 (24:1)	59.4±6.90	Histopathologic or CT, MRI	19	12	One day
Haojun Chen	2020	retrospective	34 (25:9)	60.6 (33-75)	Histopathologic or radiographic follow-up	14	9	<1 Week
Li Huo	2020	prospective	20 (18:2)	58.0 (43-78)	Histopathologic or radiographic follow-up	9	7	within 3 days

Author	Year	Cases	Intrahepatic lesions	^{18}F-FDG				^{68}Ga-FAPI			
				TP	FP	FN	TN	TP	FP	FN	TN
Dheeratama Siripongsatian	2022	21	43	16	1	25	1	41	2	0	0
Lunxiu Qin	2021	25	39	20	1	15	3	30	3	5	1
Haojun Chen	2020	32	54	25	0	23	6	41	0	7	6
Li Huo	2020	20	23	11	0	9	3	20	0	0	3

	Classification	TBR ^{18}F-FDG (Intrahepatic)	TBR FAPI (Intrahepatic)	P1	SUVmax ^{18}F-FDG (Intrahepatic)	SUVmax FAPI (Intrahepatic)	P2
2022	HCC 14 CCA 13	Total: 1.69 HCC: 1.96 (1.25-6.95) CCA: 1.47 (0.98-7.74)	Total: 15.90 HCC: 7.90 (2.03-13.54) CCA: 21.08 (3.59-35.18)	<0.05	Total: 5.17 HCC: 5.53 (3.37-23.23) CCA: 4.89 (3.38-23.23)	Total: 15.61 HCC: 9.65 (4.98-18.89) CCA: 19.82 (5.27-30.25)	<0.05
2021	HCC 25	3.14±1.59	11.90±8.35	<0.05	5.89±3.38	6.96±5.01	>0.05
2020	HCC 20 CCA 12	Total: 1.17 (0.89-4.41) HCC: 1.16 (0.96-4.21) CCA: 1.49 (0.89-4.41)	Total: 5.55 (1.05-10.62) HCC: 4.97 (1.05-10.49) CCA: 6.95 (2.15-10.62)	<0.05	Total: 4.24 (2.63-11.26) HCC: 4.28 (3.25-10.81) CCA: 4.22 (2.63-11.26)	Total: 13.61 (4.66-23.21) HCC: 11.47 (4.66-21.03) CCA: 16.51 (8.34-23.21)	<0.05
2020	HCC 16 CCA 4	Total: NR HCC: 2.39 (1.12-10.09) CCA: 4.42 (2.42-6.74)	Total: NR HCC: 7.13 (2.32 -21.15) CCA: 26.4 (21.50-30.92)	<0.05	Total: NR HCC: 4.86 (2.55 -16.34) CCA: 9.19 (4.60 -12.80)	Total: NR HCC: 8.47 (2.25 - 15.54) CCA: 14.1 (11.18-15.86)	<0.05

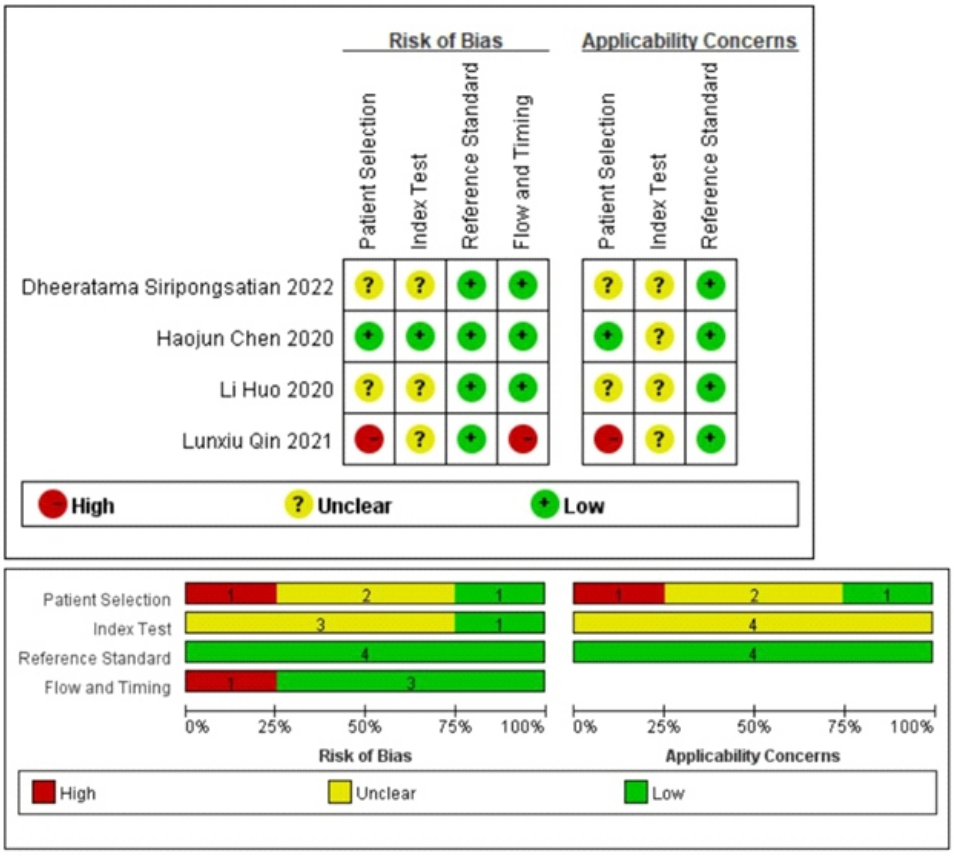

Figure 2. Risk bias evaluation of included studies

Results of meta-analysis

Threshold effects and heterogeneity of results

1) ^{18}F-FDG PET/CT: The threshold effect result of ^{18}F-FDG PET/CT in the diagnosis of primary liver cancer was r= -0.2, P=0.8, indicating that there was no significant threshold effect. Heterogeneity results: Psen=0.4, I^2sen=0.00%; Pspe= 0.24, I^2spe=28.28%, indicating that there is no obvious heterogeneity between Sen and Spe in the four included studies.
2) ^{68}Ga-FAPI PET/CT: The threshold effect result of ^{68}Ga-FAPI PET/CT in the diagnosis of primary liver cancer was r=0.5, P= 0.667, indicating that there was no significant threshold effect. Heterogeneity results: Psen=0.01, I^2sen=76.32%; Pspe= 0.01, I^2spe=76.41%, indicating that there is high heterogeneity in Sen and Spe in the four included studies, so a random effect model was used for combined effect analysis.

Meta-analysis results

1) ^{18}F-FDG PET/CT: ^{18}F-FDG PET/CT diagnosis of primary liver cancer intrahepatic lesions: Sen=0.5 (95%CI: 0.41-0.59), Spe=0.87 (95%CI: 0.52-0.98), PLR=3.99 (95%CI: 0.76-20.85), NLR=0.57 (95%CI: 0.42-0.78), DOR=6.99 (95%CI: 1.01-48.43) and AUC=0.58 (95%CI: 0.53-0.62).
2) ^{68}Ga-FAPI PET/CT: ^{68}Ga-FAPI PET/CT diagnosis of primary liver cancer intrahepatic lesions: Sen=0.96 (95%CI: 0.73-0.99), Spe=0.76 (95%CI: 0.01-1.00), PLR=3.93 (95%CI: 0.05-285.18) , NLR=0.06 (95%CI: 0.01-0.50), DOR=68.21 (95%CI: 0.25-18726.09), AUC=0.96 (95%CI: 0.94-0.98).

The Sen, Spe and AUC values of the meta-analysis results of the two groups of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT were compared and analyzed. The Sen of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT in the diagnosis of primary liver cancer was statistically different (P=0.02), ^{68}Ga-FAPI was higher than ^{18}F-FDG, but there was no significant difference between Spe and AUC (P=0.538, P=0.317). As shown in Table 4 and Figures 3-4.

Table 4. *Comparison of diagnostic value about ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT.*

Diagnosis	SEN (95%CI)	SEP (95%CI)	+LR (95%CI)	-LR (95%CI)	DOR (95%CI)	AUC (95%CI)
^{18}F-FDG	0.5 (0.41-0.59)	0.87 (0.52-0.98)	3.99 (0.76-20.85)	0.57 (0.42-0.78)	6.99 (1.01-48.43)	0.58 (0.53-0.62)
^{68}Ga-FAPI	0.96 (0.73-0.99)	0.76 (0.01-1.0)	3.93 (0.05-285.2)	0.06 (0.01-0.50)	68.21 (0.25-18726.09)	0.96 (0.94-0.98)
Z	2.323	0.615	0.577	1.607	1.443	1
P	0.02	0.538	0.564	0.108	0.149	0.317

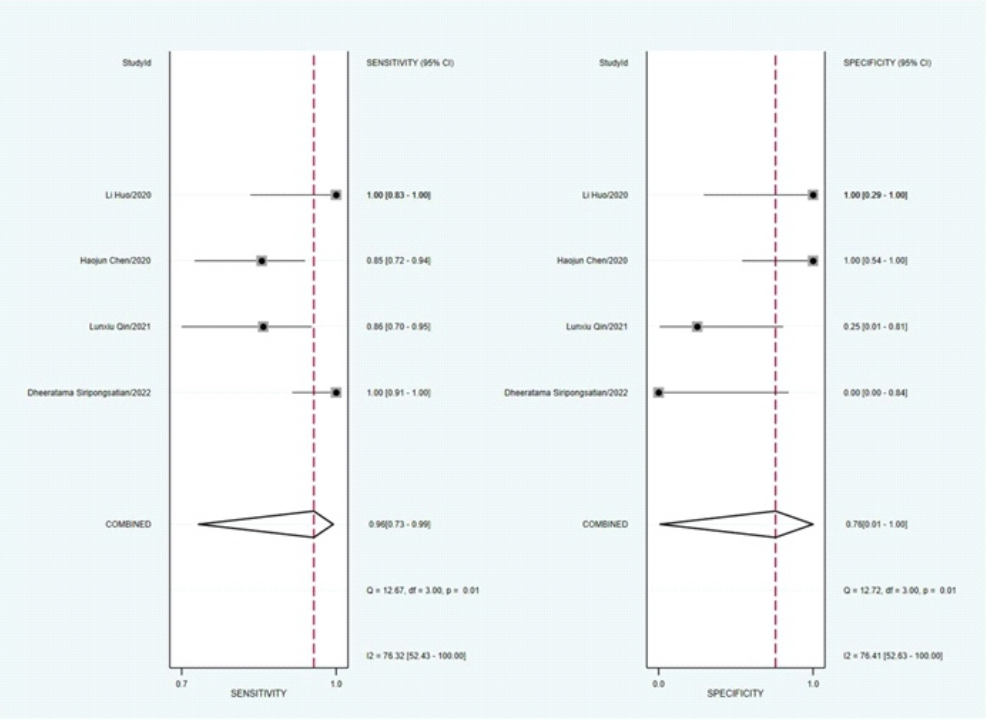

Figure 3. Forests of Sen and Sep about ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT in diagnosing primary liver cancer

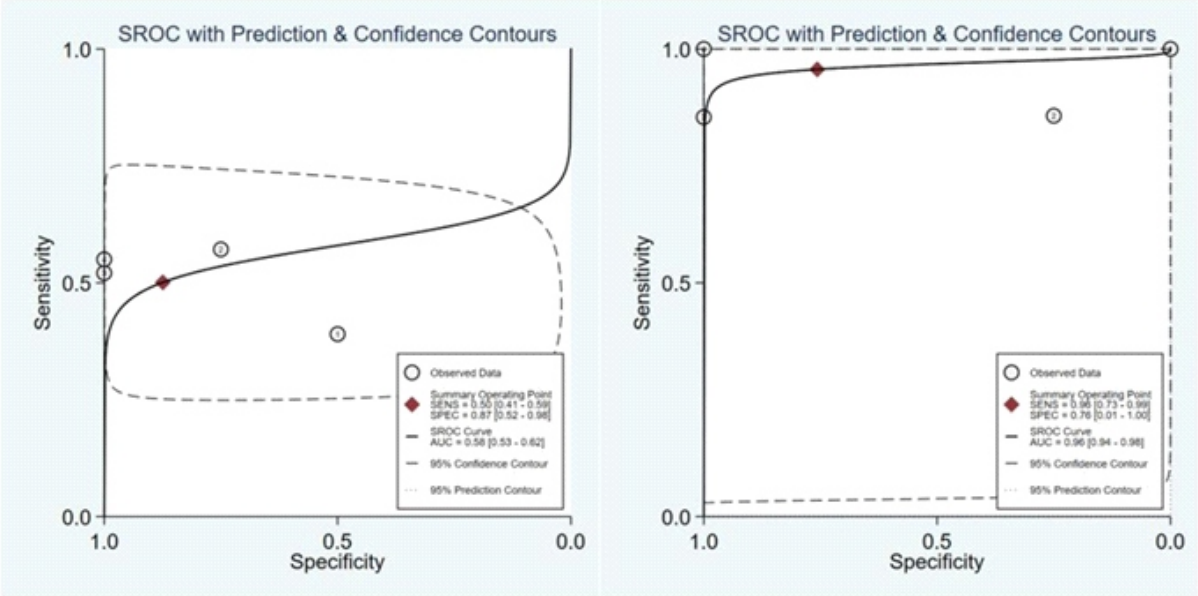

Figure 4. SROC about ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT in diagnosing primary liver cancer

Table 5. *Pooled results of TBR and SUVmax in primary liver lesions.*

Diagnosis	TBR HCC (95%CI)	SUVmax HCC (95%CI)	TBR CCA (95%CI)	SUVmax CCA(95%CI)
^{18}F-FDG	2.19(0.89-3.49)	5.21(4.18-6.25)	1.91(0.72-3.11)	5.47(2.59-8.36)
^{68}Ga-FAPI	8.07(6.15-9.99)	7.81(6.17-9.45)	17.78(3.17-32.40)	15.07(12.21-17.93)
Z	2.309	2.309	1.964	1.964
P	0.021	0.021	0.053	0.053

SUVmax and TBR

The pooled results show that in HCC, FAPI was greater than ^{18}F-FDG in TBR an SUVmax , with significant difference (P= 0.021); In CCA, FAPI was greater than ^{18}F-FDG in both TBR and SUVmax, but there was no significant difference (P= 0.053). As shown in Table 5.

Deeks funnel plot to detect publication bias

The results in Figure 5 suggest that the P values of the publication bias coefficients in the 4 studies on the diagnosis of primary liver cancer by ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT were 0.07 and 0.72, respectively. There was no obvious publication bias in the included studies of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT in the diagnosis of primary liver cancer.

Discussion

At present, ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT imaging play a vital role in the diagnosis and management of various malignancies. However, ^{18}F-FDG has limited value in the early diagnosis of HCC because of its low sensitivity [28, 29]. Gallium-68-FAPI PET/CT, as a new and promising imaging technology, has showed encouraging diagnostic efficacy in the study of liver cancer, but since most of the trials are small samples and mostly retrospective, there are no systematic reviews of diagnostic value of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT. This meta-analysis evaluated and compared the diagnostic value of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT in patients with liver cancer from studies published so far. The results showed that the high sensitivity (Sen=0.96, 95% CI:0.73-0.99) and specificity (Spe=0.76, 95%CI:0.01-1.00) of ^{68}Ga-FAPI-04 PET in detecting primary liver cancer. The sensitivity of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT in the diagnosis of primary liver cancer was statistically different (P= 0.02), ^{68}Ga-FAPI was higher than ^{18}F-FDG, but there was no significant difference between Spe and AUC (P=0.538, P= 0.317). This indicates that both of the two imaging techniques have certain diagnostic value for primary liver cancer, but compared with ^{18}F-FDG PET/CT, ^{68}Ga-FAPI PET/CT could correctly identify both primary and metabolic liver tumors

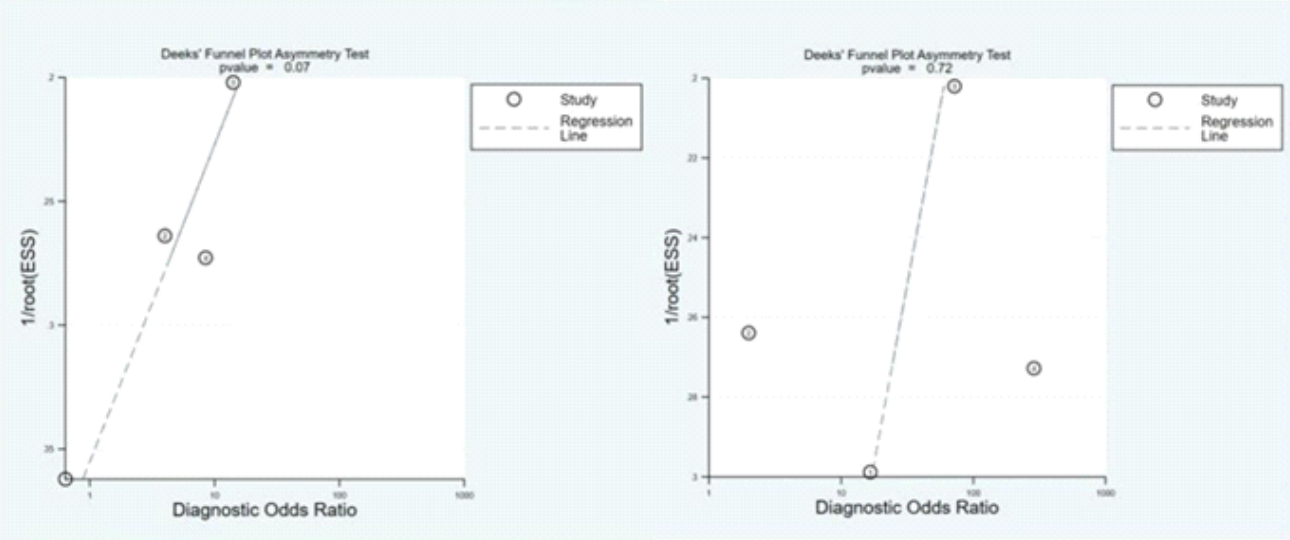

Figure 5. Deeks funnel chart to detect publication bias.

with a higher sensitivity, which might improve liver cancer staging and follow-up treatment. The result could be attributed to the higher uptake of ^{68}Ga-FAPI by the tumors and the relatively lower background uptake activity of ^{68}Ga-FAPI in liver parenchyma. In our study, the pooled results show that in HCC, ^{68}Ga-FAPI was greater than ^{18}F-FDG in TBR and SUVmax, with significant difference (P=0.021). This is due to the low level of expression of glucose transporter 1 and glucose transporter 3 [10] results in some HCC lesions being ^{18}F-FDG non-avid on PET. Correspondingly, In CCA, ^{68}Ga-FAPI seems greater than ^{18}F-FDG in both TBR and SUVmax, but there was no significant difference (P=0.053). This is a finding worth pondering. Considering the small sample size and large variation in uptake value the result of our study informational purposes only. Conclusive evidence on whether there is an uptake difference between ^{18}F-FDG and ^{68}Ga-FAPI is subject to further research.

Additionally, we noted that ^{68}Ga-FAPI uptake was higher in most CCA primary lesions than in HCC lesions. Specifically, the values of both TBR and SUVmax of CCA are approximately more than twice that of HCC. This could be attributed to dense desmoplastic stroma and abundant cancer-associated fibroblasts both considered as hallmark histological features of CCA [18, 30], which could lead to higher uptake of ^{68}Ga-FAPI.

Other than the higher tracer uptake of ^{68}Ga-FAPI, the superior performance of ^{68}Ga-FAPI PET/CT could be attributed to its enhanced ability of visualizing small metastases (diameter <1.0cm). Tumor lesions with a size >1-2mm require the formation of supporting stroma. Since the stroma volume can be larger than the tumor volume, stroma targeted PET imaging may be more sensitive than glycolysis targeted PET imaging in detecting small lesions with sufficient FAP-expressing stroma. In some studies we included [24, 26, 27], more local lymph node metastases and distant metastases are detected by ^{68}Ga-FAPI PET/CT than that by ^{18}F-FDG PET/CT. Besides that, one of the included study [24] shows that higher values of TBR and SUVmax of local lymph node are more detected by ^{68}Ga-FAPI PET/CT than that by ^{18}F-FDG PET/CT. Therefore, compared with ^{18}F-FDG PET/CT, ^{68}Ga-FAPI PET/CT could be more likely contributed to the detection of primary early lesions and metastatic lesions. Only two articles introduced the uptake of local lymph nodes and their distant metastases. The sample size was small, and the information provided in the original text was insufficient, so they were not summarized and analyzed. But since neglect intrahepatic primary small lesions or underestimating extrahepatic metastases may worsen the prognosis of liver cancer, this advantage of ^{68}Ga-FAPI PET/CT may be particularly important since it may inform changes in tumor staging and subsequent disease management. It is worth mentioning that in [25] the SUVmax and TBR of ^{68}Ga-FAPI-04 in positive lesions were correlated with tumour size, especially in poorly-differentiated or undifferentiated HCC, but in [27] they only observed a significantly higher FAPI uptake in moderately differentiated HCC tumours. This is an interesting discovery. This might indicate that the uptake of ^{68}Ga-FAPI-04 in the lesions is closely related to the differentiation of HCC. Unfortunately, limited to the small sample size, it is not of universal significance, which needs to be studied in the future to clarify the relationship between HCC differentiation and uptake of ^{68}Ga-FAPI-04. Furthermore, The SUVmean of ^{68}Ga-FAPI-04 in patients with cirrhosis was significantly higher than that of patients without cirrhosis in [25], but there was no statistical difference in [27]. This might be attributed to the heterogeneity of studied patients and different degrees of liver fibrosis.

Fibroblast-activation protein expression is difficult to detect in non-diseased adult organs, but is greatly upregulated in sites of tissue remodel-ling, which include liver fibrosis, lung fibrosis, atherosclerosis, arthritis, tumours and embryonic tissues [31]. Although a high tracer uptake benefit to lesion identification, it seems that result in a higher false-positive rate. Intense ^{68}Ga-FAPI-04 uptake caused by benign lesion or operation-induced inflammation may be mistaken as tumor relapse indications. The inflammation-induced unspe-

cific fibrosis could also lead to the positive ^{68}Ga-FAPI uptake [32-34]. Therefore, the false-positive uptake of ^{68}Ga-FAPI caused by inflammation might influence determination of benign and malignant lesions. Prognostic imaging in primary liver cancer remains a challenge. In this condition, morphological characteristics in CT and MRI scans may help differentiate between inflammatory lesions and true malignancy. Therefore, other ima-ging findings and clinical data should be taken into consideration, rather than solely based on the ^{68}Ga-FAPI uptake level.

Limitations

This study also has several limitations. All included studies including three retrospective studies and one prospective study were single-arm observational studies, the sample size of the trial was small, and the risk of bias was high. In addition, these trials were heterogeneous in terms of research design, other diseases (such as cirrhosis), previous treatments, the degree of AFP expression and pathological grading of liver cancer. However, relevant clinical information and the pathological confirmation of nodal metastasis, distant metastasis, and local recurrent/residual tumour were not available, which limited the accuracy of observation and evaluation of these indicators.

In conclusion, multimodality hybrid imaging based on ^{68}Ga-FAPI could provide information on various aspects of primary liver cancer, resulting in more accurate diagnosis and evaluation. However, more high-quality original research is still needed in the future to explore the diagnostic value of ^{68}Ga in primary liver cancer.

The authors declare that they have no conflicts of interest.

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